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Title: Geo-economic variations in epidemiology, patterns of care and outcome in patients with Acute Respiratory Distress Syndrome: Insights from the LUNG SAFE prospective cohort study

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Take-home message: Patients with ARDS from European high-income countries had higher ARDS severity, received more adjunctive therapies and had a longer hospital length of stay than patients from the rest of the world high-income countries. Lower country gross national income was associated with poorer hospital survival in patients with ARDS.

Tweet: Geo-economic variations exist regarding ARDS severity, clinician recognition, management approaches, and in patient outcomes from ARDS. [140-character limit]

Abstract

Background: There is limited information about the geo-economic variations in demographics, management and outcome of patients with acute respiratory distress syndrome (ARDS).

Methods: The Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) study was conducted during four consecutive weeks in the winter of 2014 in a convenience sample of 459 ICUs from 50 countries across 5 continents. A key secondary aim was to characterize variations in the demographics, management and outcome of patients with ARDS. We compared patients across three major geo-economic groupings, namely Europe high-income (Europe-High), Rest of World high-income (rWORLD-High), and Middle-income (Middle) countries.

Findings: 1,521 (54%) of the patients were recruited from Europe-High, 746 (27%) were from rWORLD-High, and 546 (19%) from Middle countries. Significant geographic variations were demonstrated regarding patient demographics, ARDS risk factors and comorbid diseases. The proportion of patients with-severe ARDS or with P/F ratio <150 was less in rWORLD-High compared to the two other regions. Use of prone position, neuromuscular blockade and ECMO were greatest in Europe-High. Adjusted duration of invasive mechanical ventilation and ICU length of stay were shorter in patients from rWORLD-High. Higher country per capita gross national income was associated with increased hospital survival in patients with ARDS, while the middle-income countries were associated with reduced hospital survival.

Interpretation: Important geo-economic differences exist regarding ARDS severity, clinician recognition of ARDS, ARDS management approaches, and in patient outcomes. An independent association exists between per capita income and outcomes in patients with ARDS.

Trial Registration: ClinicalTrials.gov NCT02010073

Research in context

Evidence before this study

We searched PubMed in December, 2016, for articles published since Jan 1 Nov, 1990, with search terms relating to ‘acute respiratory distress syndrome’ and ‘geographic’ or ‘country’. Specific search terms used were "respiratory distress syndrome, adult"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields] AND "adult"[All Fields]) OR "adult respiratory distress syndrome"[All Fields] OR ("acute"[All Fields] AND "respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "acute respiratory distress syndrome"[All Fields]) AND geographic[All Fields] OR country[All Fields]. Searches were not limited by language and were supplemented by review of reference lists. We found some studies reporting findings from more limited regions, such as individual countries or small groups of countries, but no study reporting data regarding acute respiratory distress syndrome across major geo-economic groupings.

Added value of this study

Significant variations exist regarding patient demographics, ARDS risk factors and comorbid diseases across the 3 major geo-economic groupings, namely Europe high income (Europe-High), Rest of World high income (rWORLD-High), and Middle Income (Middle) countries. ARDS severity was less overall in Rest of World high-income countries. In terms of patterns of care, the use of prone positioning, neuromuscular blockade and recruitment maneuvers were greatest in Europe-High countries. ICU length of stay was shorter, and the likelihood of unassisted ventilation to day 28 was significantly ($P < 0.001$) higher, in rWORLD-High countries.

Lower country gross national product was associated with poorer hospital survival in patients with ARDS. The middle-income country grouping was associated with worse ARDS outcomes than either high-income country grouping.

Implications of all the available evidence

Important regional differences exist regarding the demographics, management and outcomes of patients with ARDS. These data identify opportunities to enhance implementation of evidence-based interventions that improve outcome from ARDS.

Introduction

Important geographic and economic variations in regard to the epidemiology, and patterns of care have been described for multiple diseases including diabetes [1], asthma [2], myocardial infarction [3,4], heart failure [5], atrial fibrillation [6], COPD [7], end-stage renal disease [8] and breast cancer [9]. Furthermore, the use of interventions such as blood transfusions [10], amputation [11], aneurysm repair [12] and carotid revascularization [13], and outcome following procedures such as coronary artery bypass grafting [14] also vary by region and/or socioeconomic status. Geo-economic variations in the epidemiology and management of patients with acute respiratory distress syndrome (ARDS) may have important implications for patient outcome. To date the extent and the impact of these variations have not been characterized.

The Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) study in 459 ICUs in 50 countries in 6 continents found a two-fold difference in the incidence of ARDS across the different continents [15]. ARDS was under-recognized by clinicians, while the use of evidence based ventilatory strategies and adjuncts was lower than expected. Of most concern, ARDS continues to confer a high mortality, with 40% of patients with ARDS dying in hospital.

A key secondary aim of the LUNG SAFE study was to characterize geo-economic variations in demographics, management and outcome of patients with ARDS. We compared patients across three major geo-economic groupings, namely Europe high income (Europe-High), Rest of World high income (rWORLD-High), and Middle Income (Middle) countries.

Methods and Materials

Study Design

The detailed methods has been published elsewhere [15]. In brief, LUNG SAFE was an international, multicenter, prospective cohort study, with a 4 week enrollment window in the winter season in each hemisphere [15]. The study, conceived by the Acute Respiratory Failure Section of the European Society of Intensive Care Medicine (ESICM), was endorsed by multiple national societies/networks (***Appendix 1***). All participating ICUs obtained ethics committee approval, and either patient consent or ethics committee waiver of consent. National coordinators (***Appendix 1***) and site investigators (***Appendix 2***) were responsible for obtaining ethics committee approval and for ensuring data integrity and validity.

Patients, Study Design and Data Collection

Inclusion criteria were: admission to a participating ICU (including ICU transfers) within the 4-week enrollment window; and receipt of invasive or noninvasive ventilation (NIV). Exclusion criteria were: age<16 years or inability to obtain informed consent, where required. Patients were classified as having ARDS based on the Berlin criteria [16]. To ensure a more homogenous dataset, we restricted subsequent analyses to the large subset of patients (2,813 of 3,022 patients, 93.1%) fulfilling ARDS criteria on day 1 or day 2 (n=2,813) following the onset of acute hypoxemic respiratory failure (AHRF) [***Figure 1***] that received invasive mechanical ventilation (MV) or non-invasive ventilation (NIV). Data from the first day of fulfillment of ARDS criteria were used in these analyses.

Data Definitions

We used the 2016 World Bank countries classification, which accounts for the gross national income per capita (*http://databank.worldbank.org/data/home.aspx*) to define 3 major geo-economic groupings: Europe high income (Europe-High), Rest of World high income (rWORLD-High), and Middle Income (Middle) countries for this analysis (***Table 1***).

Duration of invasive ventilation was calculated as the number of days that the patient required invasive mechanical ventilation up to day 28. Driving pressure was defined as plateau pressure minus PEEP. Plateau and driving pressure analysis confined to patients (n=742) in whom plateau pressure was measured and in whom there was no evidence of spontaneous ventilation (i.e. when set and measured respiratory rates were equal). All modes other than volume and pressure control modes were considered to permit spontaneous breathing. Mortality was evaluated at 28-days, ICU and hospital discharge (or to day 90, whichever event occurred first).

Data Management and Statistical Analyses

Descriptive statistics included proportions for categorical and mean (standard deviation) for continuous variables. The amount of missing data was low [15], and no assumptions were made for missing data. Data were unadjusted unless specifically stated otherwise. Differences among geo-economic groupings were evaluated using chi-square test (or Fisher exact tests) and ANOVA or Kruskal–Wallis test as appropriate. The Shapiro-Wilk test was used to assess normality in data distribution. Bonferroni correction was applied to determine significance in the setting of multiple comparisons.

Kaplan-Meier analysis was used to estimate the likelihood of liberation from invasive mechanical ventilation and of hospital mortality within 28 days of AHRF onset. We assumed that patients discharged alive from hospital before 28 days were alive at day 28. The comparison among geo-economic groupings was performed using the log-rank test.

We used mixed effect logistic regression to evaluate the association between mortality and ICU-level predictors. We considered a two-level random intercept model for binary responses: the first level was represented by individuals and the second level by the ICUs. Demographic, risk, illness severity and management factors were considered at the first level; gross national income (GNI) per capita, geographic area and ICU characteristics (number of beds, academic ICU, beds per nurse, beds per physician, and percentage of ICU beds in hospital) were used as predictors at the second level. Since some ICUs had few observations to support the normal assumption of the model, we applied the bootstrap method (1,000 samples randomly extracted) to estimate the model parameters, odds ratio (ORs) and the confidence intervals (CIs). The individual predictors (level one) were identified through the stepwise approach (forward and backward selection combined with a significance level of 0.05 both for entry and retention) applied to a logistic regression. These predictors were included in a mixed effect logistic regression model and then, one by one, we evaluated the statistical significance of each ICU variable (level two). Analogously, we applied the mixed effect Poisson regression to evaluate the association between ICU-level predictors and ICU length of stay and duration of invasive mechanical ventilation.

Statistical analyses were performed with R, version 3.0.2 (R Project for Statistical Computing, (http://www.R-project.org) and SAS software, version 9.4 (SAS Institute, Cary, NC, USA). All p-values were two-sided, with p-values <0.05 considered as statistically significant. The study protocol, case report form and full statistical analysis plan are included in ***Appendix 3.***

RESULTS

Of the 12,906 patients screened for the LUNG SAFE study, 2,813 (22%) fulfilled ARDS criteria at day 1 or day 2 following enrollment. Of these, 1,521 (54%) were recruited from Europe-High, 746 (27%) from rWORLD-High, and 546 (19%) from Middle countries [***Figure 1***]. ARDS comprised 23% of screened patients in Europe-High, compared to 21% in both rWORLD-High and in Middle countries [***Table 1***]. Overall, (298 of 459) 65% of participating ICUs were in academic hospitals, with a median of 14 beds per ICU, and a median nurse to bed daytime ratio of 0.6, and physician to bed ratio of 0.3. Table 1 details the number of ARDS patients enrolled by country and geo-economic region, and data on the structure and organization of participating ICUs.

Patient Demographic Characteristics

Patients from Europe-High countries were significantly older, and there was a stepwise increase in body mass index in patients from Middle to Europe-High to rWORLD-High countries. Diabetes mellitus, chronic renal failure and liver disease were significantly more frequent in rWORLD-High countries, while congestive heart failure was highest in patients from Middle countries [***Figure e1A***]. Pneumonia was the dominant risk factor for ARDS across each group [***Figure e1B***]. Extra-pulmonary sepsis was highest in Middle countries, while differences were also seen regarding, trauma, inhalational injury, pancreatitis, and the absence of risk factors [***Figure e1B***].

Patient Illness Severity

ARDS severity varied by region, with mild ARDS significantly higher and severe ARDS significantly lower in rWORLD-High compared to the Europe-High or Middle countries [***Table 2; Figure e1C***]. rWORLD-High had a significantly lower proportion of patients with a P/F ratio <150 and a lower proportion of patients with persistent severe ARDS compared to both Europe-High and Middle countries [***Table 2***]. Mean P/F ratios were significantly higher in rWORLD-High while non-pulmonary SOFA scores were lower in Europe-High countries [***Table 2***].

Clinician Recognition of ARDS

Clinician recognition of mild and moderate, but not severe, ARDS was lower in rWORLD-High compared to the Europe-High or Middle countries [***Table 3***].

Ventilator Management of ARDS

In rWORLD-High countries, more patients (66%) received lower tidal volumes (≤8 mL/kg PBW) compared to 62% in Europe-High and Middle countries [***Figure 2A***]. Plateau pressure measurement was highest in patients from Middle countries [***Table 3***]. The distribution of plateau pressures and driving pressures were similar in Europe-High and the rWORLD-High, but differed in Middle countries, with 18% of patients having a driving pressure <7.5 cmH_2O [***Figure 2B-C***]. Over 50% of patients in Middle countries had a PEEP <7.5 cmH_2O, compared to 44% in Europe-High and 40% in rWORLD-High, respectively [***Figure 2D***]. The proportion of patients receiving 'protective' ventilation, defined as a tidal volume ≤8 mL/kg PBW and plateau pressure of ≤30 cmH_2O, was not different across the geo-economic groupings [***Table 3***].

Spontaneous ventilation in early ARDS was significantly more frequent in patients from rWORLD-High countries compared to Europe-High [***Table 3***]. Inspired oxygen use differed by region, with lower FiO_2 ($FiO_2 \leq 0.4$) greater in rWORLD-High countries, and higher FiO_2 more frequent in Europe-High countries [***Figure 2E***]. Hypercapnia was more frequent in patients from Europe-High countries, while hypocapnia was more frequent in patients in Middle countries [***Figure e2A***]. Modes of ventilation differed, with least use of pressure support and greatest use of SIMV in Middle countries. Use of volume and pressure control ventilation modes was similar across the geo-economic groupings [***Figure e2B***].

Use of adjunctive measures

There was no significant variation in the use of NIV [***Figure 2F***]. The use of neuromuscular blockade, and prone positioning in all patients and in the subgroup with a P/F ratio <150 [Table e1] were significantly higher in patients from Europe-High countries. ECMO use in patients was significantly lower in the Middle countries. Use of recruitment maneuvers was lower in rWORLD-High countries. Adjustment for ARDS severity did not explain the regional differences in the use of adjunctive measures.

Outcome from ARDS

Unadjusted duration of invasive ventilation and ICU length of stay were lower in rWORLD-High countries [***Table e2***]. Kaplan-Meier analyses demonstrated significant differences in the probability of weaning from invasive ventilation at each level of ARDS severity [***Figure 3 and e3***]. Probability of weaning was greater in patients from rWORLD-High countries compared to Europe-high ($P < 0.001$, log rank test) and middle-income countries ($P < 0.001$, log rank test). Multivariate analyses demonstrated that the adjusted incidence rate ratio for duration of invasive mechanical ventilation, and ICU length of stay was significantly higher in Europe-High countries, but not Middle countries, compared to rWORLD-High countries [***Figure 4; Tables e3-4***].

Unadjusted ICU and hospital mortality were both lower in rWORLD-High countries [***Table e2***]. Kaplan-Meier analyses demonstrate that 28-day survival was highest in rWORLD-High countries, and lowest in Middle countries [***Figure 3***]. Multivariate analyses demonstrated that the adjusted incidence rate ratio for ICU and hospital survival significantly better in rWORLD-High and Europe-High, countries, compared to Middle countries [***Figure 4; Tables e5-6***]. There was no impact of differences in approaches to mechanical ventilation on ICU or hospital mortality by geo-economic region [***Tables e5-6***]. Patient level variables associated with hospital mortality included age, active or hematologic neoplasm, chronic liver failure, acidosis, P/F ratio, non-pulmonary SOFA score, and respiratory rate. There was no independent association between ICU level variables, including ICU size, beds per nurse/physician, and the percentage of academic ICUs, and hospital mortality [***Tables e5-6***].

A separate multivariate analysis across all countries (i.e. without any grouping), and using per capita GNI as a continuous variable, demonstrated that outcome from ARDS is independently associated with GDI [***Table 4***]. Respiratory (42%) and cardiovascular failure (37%) were the most common factors leading to ICU death, with no significant geographic variation seen [***Table e7***]. Decisions around limitation of life sustaining measures were less frequent in Middle (17%) compared to Europe-High (27%) or rWORLD (26%) countries.

Discussion

In this prospective observational cohort study, we found important differences in ARDS severity patterns, the extent of clinician recognition, and approaches to management of patients with ARDS across geo-economic regions. Patients from Europe-High countries had longer durations of mechanical ventilation and ICU stays compared to patients from rWORLD high countries. We demonstrate for the first time to our knowledge that indices of national socioeconomic status are associated with patient survival from ARDS.

While there were significant demographic differences among the patients from the 3 geo-economic regions, the impact on patient outcome appears limited. The older age of patients from Europe-High countries may partly explain the higher unadjusted mortality in this region, as age was independently associated with hospital mortality in this and in prior studies [17-19]. Of the pre-existing comorbidities associated with poor outcome, only chronic liver failure, was different, being higher in rWORLD-High countries. The pattern of critical illness seemed to differ, with patients from Europe-High countries having greater ARDS severity, and a higher proportion with persistent severe ARDS, while patients from rWORLD-High countries had more severe systemic illness. As has previously been demonstrated, both ARDS severity and non-pulmonary SOFA scores were independently associated with hospital mortality [19].

The greater use in Europe-High countries of neuromuscular blockade and prone positioning in patients with a P/F ratio <150, may reflect the fact that the evidence for these approaches was largely developed in Europe-High countries [20,21], and may have penetrated to a lesser extent in the rest of the world. Other possible explanations include the unavailability of cisatracurium in some countries, and lack of ‘hands-on’ experience with prone positioning. Even in Europe-High countries, however, prone positioning was used in <10% of patients with P/F <150, the population in which proning improves outcome [20]. A large clinical trial is being conducted in the US by the PETAL network [ROSE trial, NCT02509078] to address any ongoing scientific uncertainty regarding the efficacy of neuromuscular blockade in ARDS. These variations in the use of adjunctive measures are not explained by differences in ARDS severity profile, by economic differences (with the possible exception of ECMO, which was used less in middle-income countries), or by differences in ARDS recognition. The lack of regional variation in the use of NIV suggests that barriers to the use of adjuncts can be addressed [22]. Understanding and addressing local barriers and facilitators to the implementation of simple and relatively inexpensive adjunctive measures, such as prone positioning and neuromuscular blockade, should be prioritized, given their potential to improve survival from ARDS.

Patients from Europe-High countries required longer durations of mechanical ventilation and longer ICU stays compared to patients from countries of similar levels of wealth outside Europe. These differences persisted after adjustment for ARDS severity and other covariates. Importantly, we did not find any association between ICU level variables and outcome from ARDS, suggesting that the differences in ICU organization and/or staffing do not explain the effect of income. This suggests that differences in approaches to ARDS management may have important implications for these highly patient-centered outcomes. Potential explanations include the fact that the proportion of patients that received larger tidal volumes was lowest in rWORLD-High countries and highest in Europe-High countries, a concern given that higher tidal volume was associated with worse outcome in these patients[23]. The greater use of higher FiO_2 in patients from Europe-High countries is also a concern given the recent demonstration that use of high FiO_2 in the critically ill may be harmful[24]. Other potential explanations include differences in practices surrounding weaning from ventilation, but we do not have any data to examine this issue. Interestingly, clinician recognition of ARDS was marginally lower in rWORLD countries, although the difference was least marked for severe ARDS. Decision making around limiting life sustaining measures was similar in Europe-High and rWORLD-High countries, so this is unlikely to explain these differences. Better understanding of the reasons underlying differences in the approach to the use of lower tidal volume ventilation, inspired oxygen concentrations, and adjuncts to ventilation, may facilitate further improvement of these patient relevant outcomes in patients with ARDS.

Respiratory failure and cardiovascular failure were the most important factors leading to death in the ICU, across all regions. This contrasts to some degree with prior studies suggesting respiratory failure is less commonly the cause of deaths from ARDS [25,26]. However, these studies did define respiratory failure relatively narrowly, confining it to severe gas exchange failure. They also attributed deaths to syndromes such as sepsis as well as to organ failures. We limited the list of possible factors to the different organ systems, and did not ask for a ‘cause of death’ per. Possible additional explanations for our findings include improvement in outcomes from the shock phases of critical illness [27], and potentially the increasing role of decision making to limit life sustaining measures where these are deemed futile.

The demonstration that national-level indices of wealth are associated patient survival from ARDS is a novel and provocative finding. It does not appear to be explained by differences in ICU organization or staffing. This association does not necessarily reflect a different quality of care or resources in the ICU but may reflect a lower access to critical care services or preventative medicine [28]. The latter is supported by data that residents from lower income areas have significantly higher rates of ICU admission [29], and often with higher severity of illness [30]. These data build on a growing body of evidence demonstrating the effect of socioeconomic status on survival from illness. Similar effects of income on patient survival have been demonstrated in patients with sepsis [31,32], underlining the impact of economic status on outcomes from critical illness. In patients with diabetes, the percentage of deaths attributable to high blood glucose or diabetes that occurs prior to age 70 is higher in low- and middle-income countries than in high-income countries[1]. Socioeconomic differences contributed to outcome in patients with COPD in China [7]. In an analysis of health administrative data from Ontario, Canada, asthma-specific mortality rates were 60% higher among those in the lowest compared with highest socioeconomic status [33]. In patients following acute myocardial infarction in Italy, lower levels of education were associated with increased odds of 30-day mortality[34]. Socioeconomic status also contribute to survival rates in patients with breast cancer[35]. These data present a significant public health challenge, as they further highlight the disadvantages of lower socioeconomic status on outcomes from diverse major medical conditions. Future studies are needed to elucidate the mechanisms by which difference in socioeconomic status mediate differences in outcome, so that targeted interventions can be designed and evaluated.

Limitations: This study has a number of limitations. Our patient cohort is a convenience sample, and therefore may not be representative of actual clinical practice in ICUs across the globe. This could lead to bias in results, particularly where certain types of ICUs e.g. academic ICUs may be over-represented. We did not have any low-income countries in our study, perhaps underlining the resource dense nature of critical care. Our focus on winter months does not allow us to obtain annual incidence figures for ARDS since previous studies have demonstrated an increased incidence of ARDS in the winter months. We did not have access to the source data for the patients in the enrolling ICUs, and it is possible that not all patients with ARDS in participating centers were enrolled. However, enrollment of patients with ARDS from participating ICUs met expectations based on their recorded 2013 admission rates, while data from lower recruiting ICUs was not different from that from higher enrolling ICUs, suggesting the absence of reporting biases. We instituted a robust data quality control program in which all centers were requested to verify data that appeared inconsistent or erroneous. While we have adjusted our analyses to account for known measured confounders, the possibility remains that some of our findings may arise from unmeasured or residual confounding. Lastly, our assumptions that patients discharged from the hospital before day 28 were alive at that time point, and that inpatients at day 90 survived to hospital discharge are further limitations.

Conclusions: Important geo-economic differences exist regarding ARDS severity, clinician recognition of ARDS, and the management of ARDS. An independent association exists between per capita income and outcomes in patients with ARDS.

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Figure legends:

Figure 1: Flowchart of the study population

§ Patients could have more than one cause for AHRF

‡ This is the number of patients included in the primary analysis

Figure 2: Ventilator management of patients with ARDS by geo-economic region, including distribution of tidal volume (***Panel A***), plateau pressures (***Panel B***), driving pressures (***Panel C***), PEEP (***Panel D***), fractional inspired oxygen (***Panel E***), and adjunctive measures (***Panel F***).

* Indicates between region differences

Figure 3: Kaplan-Meier survival curves of probability of weaning from mechanical ventilation (***Panel A***), and of hospital survival (***Panel B***) by geo-economic region.

Note: Patients discharged before Day 28 were assumed to be alive and off invasive MV on that day.

HR: Hazard ratio; HRs were estimated through Cox Proportional Hazard Models and we used rWORLD-HIGH as the reference category.

Figure 4: Plots of the adjusted IRRs and 95% confidence intervals for duration of mechanical ventilation and ICU length of stay (***Panel A***), and adjusted ORs and 95% confidence intervals of ICU and hospital mortality (***Panel B***) for each geo-economic area.

Note: rWORLD-High is the reference point for Panel A and Middle as reference for Panel B.

Abbreviation: IRR, *incidence rate ratio; OR, odds ratio.*

ONLINE FIGURES

Figure e1: Patient demographics and ARDS severity profile by geo-economic region.

Panel A: Frequency of pre-existing comorbidities.

Panel B: Frequency of ARDS risk factors.

Panel C: Frequency of ARDS severity categories.

* Indicates between region differences

Figure e2: Distribution of arterial PCO_2 tensions (***Panel A***) and modes of ventilation (***Panel B***) by geo-economic region.

* Indicates between region differences

Figure e3: Kaplan-Meier survival curves of probability of weaning from mechanical ventilation (***Panel A***), and of hospital survival (***Panel B***) in patients with mild, moderate and severe ARDS by geo-economic region

Note: Patients discharged before Day 28 were assumed to be alive and off invasive MV on that day.

HR: Hazard ratio; HRs were estimated through Cox Proportional Hazard Models and we used rWORLD-HIGH as the reference category.